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Primary prevention: Do the very elderly require a different approach?

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Primary Prevention: Do the very elderly require a different approach???

ABSTRACT

Recent cardiovascular prevention guidelines place a greater emphasis on randomized placebo-controlled trial data as the basis for recommendations. While such trial data are sparse for people over age 75 or 80, data demonstrate altered risk-benefit relationships in these older patients. Primary prevention strategy decisions should consider estimated life expectancy and overall function as well as cardiovascular event risks, magnitude and time to benefit or harm, potentially altered adverse effect profiles, and informed patient preferences. Data support treatment of systolic hypertension to reduce stroke, cardiovascular events and dementia in older patients with at least a 2 year estimated lifespan with modifications in systolic blood pressure goals and a need for greater attention to non-cardiovascular side effects such as falls in the very old. Lowering of elevated cholesterol levels with HMG CoA reductase inhibitors for primary prevention in people over age 75 years requires greater individual considerations as benefits may not accrue for 3-5 years and the potential impact of adverse effects. There is a rationale for lipid lowering treatment in the more highly functional older patient with cardiovascular (especially stroke) risk higher than side effect risks in the near term and with an estimated lifespan longer than the time to benefit. Aspirin has higher side effect risks and requires a longer time to achieve benefit. Trial data are lacking on exercise interventions but multi-system benefits have been shown in older patients such that exercise should be part of a preventive regimen. Preventive therapy in the very old means considering not only medical issues of co-morbidities, polypharmacy, altered risk-benefit relationship of medications but adjusting goals and approaches across the older agespan in keeping with informed patient preferences.

INTRODUCTION

High morbidity and mortality from cardiovascular disease warrant approaches to prevention and treatment that are effective in older people. Most data from gold standard highest level of evidence on cardiovascular disease prevention in the "elderly" have been collected from people 60-74 years of age, with women and minorities under-represented. Despite physiologic variability in people of the same chronologic age, on average, a 65 year old differs significantly from an 80 year old. People aged 65-75 are "younger" elderly who usually do not display the multiple medical co-morbidities or frailty or difficulty with activities of daily living, or dementia that become much more common after age 75 or 80. It is not a foregone

conclusion that preventive interventions will have the same desired or unwanted effects in all people over age 65 years. When contemplating strategies to prevent cardiovascular disease in older people it is important to consider both likelihoods of benefit as well as harm within the lifespan and functioning of the person and to incorporate individual preferences for care and risks of interventions. The purpose of this review is to present the existing clinical trial data and guidelines on treatment of systolic hypertension and elevated cholesterol for cardiovascular disease prevention in the elderly as well as data on exercise and aspiring, and to provide a perspective for decision-making for areas in which data are limited or non-existent.

Lifespan Considerations

In the U.S., the "average" 75 year old man has a life expectancy of slightly over 10 years, one of 6 years at age 85 and 4 years at age 90. The "average" 75 year old woman's life expectancy is about 12 years and decreases to about 7 years at age 85 and to 5 years at age 90. It is important, however, to recognize that the average represents only a small fraction of the population. In developed countries, most people in their 60s and early 70s are still fit, active, and able to care for themselves while those older than 75 or 80 years have increasing prevalence of frailty, limitations in the ability to independently perform activities of daily living (bathing and showering, dressing, Eating/feeding (including chewing and swallowing), functional mobility (moving from one place to another while performing activities), personal hygiene and grooming (including brushing/combing/styling hair) and toilet hygiene) , multiple chronic conditions and cognitive impairment. Gerontologists variably define older age sub-groups to identify younger old (60-69 or 65-74 years), middle-old (70-79 or 75-84 years), and very old as over 80 or 85 years of age to reflect these physiologic changes. Cardiologists and other clinicians often simplify older age classifications to two groups—younger old as those up to age 75-80 and very old as those over age 80.

Non-cardiovascular causes of death or risk factors for death become more important at older ages and quality of life and functional independence assume more importance. In fact, everyday functional capacity is a major determinant of estimated life expectancy in the very old while traditional cardiovascular risk factors are not. [1, 2] Logically, cardiovascular event risk calculators for 10 year or longer projections then have less of a role in decision-making for patients over age 75-80 years than in younger people.

Figure 1 illustrates the relationships between life expectancy and chronic co-morbid illnesses, heart failure, or impairment in mobility or activities of daily living in data collected from two representative samples of older men and women living in the U.S. [3, 4] It demonstrates the wide variation from average life expectancy. In addition to showing the impact of increasing medical co-morbiditiesor heart failure, it also demonstrates the reductions in life expectancy related to functional impairments. Older people with impairment in performing activities of daily living have a prognosis approximating or worse than that for heart failure and high medical co-morbidity. Life expectancy estimates can be calculated from government or insurance company data (see www.sssa.gov/cgi-gin/longevity.cgi, http://www.northwesternmutual.com/learning-center/the-longevity-game.aspx) or from longitudinal studies of aging for older and very old people. [1, 2] A calculator developed for the very old that incorporates functional assessment and living site of the older person to determine likelihood of survival for periods from 1 to 4-10 years can be found at http:/ePrognosis.ucsf.edu. A review of noncancer patients with a median survival of six months or less identified a universal set of prognostic factors that included poor functional status, advanced age, malnutrition, co-morbid illnesses, organ dysfunction, and hospitalization for acute compensation. [5] Individualized estimates of life expectancy should be a

factor when considering prevention strategies as time to benefit may vary and may not be within the anticipated lifespan of the older person while adverse effects may be more immediate.

1. Hypertension

A. Prevention Trial Data.

It is somewhat difficult to clearly separate data on secondary prevention from data on primary prevention as most trials enrolled some patients with prior stroke or transient ischemic attack, or stable cardiovascular disease.(see Table 1) [6-12] Similarly, many of the trials enrolled participants with diastolic hypertension in combination with systolic hypertension. Diastolic hypertension does not increase with age and treatment has age-independent benefits. Systolic hypertension increases in prevalence with aging and benefits of treatment have been shown in randomized placebo-controlled trials. Initially, data on older age groups were analyzed as subsets from larger clinical trials of all age groups. (see Table 1) Over time, upper age cutoffs were removed from most large studies, women were included, and studies focused on older people with analysis of cognitive as well as cardiovascular endpoints.

Lowering elevated systolic blood pressure (SBP) generally produces greater reduction in stroke events and heart failure than coronary artery disease (CAD). (see Table 1). Benefits may occur as soon as 1-2 years after treatment begins. At least two large trials in the elderly [9, 10] were terminated prematurely after a mean duration of 2 years as stroke benefit outcomes were met.[8-10, 13] In the international Hypertension in the Very Elderly Trial (HY-VET) study of highly functional patients over age 80, the number needed to treat (NNT) was 94 to prevent one stroke after 2 years. [10] In primarily younger elderly hypertensives (see Table 1), NNT varied from 23-33 after 4-5 years in other trials. When analyses were performed separately for participants with prior cardiovascular events, greater benefit of SBP lowering was seen in patients with a history of stroke. [13] Death or prolongation of life have not usually been primary or secondary endpoints.

The clinical trials differ in both target SBP and achieved SBP. Table 1 presents BP levels achieved in randomized placebo-controlled trials. In the trials, both treatment and placebo groups had blood pressure lowering. [8-10] Placebo groups had mean SBP decrease from 155 to 163mmHg compared to decreases to 144-152 mmHg with active treatment. The Study on

Cognition and Prognosis in the Elderly (SCOPE) trial, amended to allow treatment in the control group during the study, reduced pressures from 166.5/90.4 to 148.5/81.6 mmHg in controls, and from 166/90.3 mmHg to 145.2/79.9 with candesartan and reported significantly better outcomes with candesartan. [12] Thus, some argue that achieving SBP of 144-152 mmHg would replicate the SCOPE results and further suggest that the target SBP be closer to 145 than 150.

The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) directly compared lowering SBP more intensively (means of 135.9/74.8 mmHg) to less intensively (145.6/78.1 mmHg) with efonidipine [14]. No benefit with more intense control was found for any cardiovascular endpoint, including stroke. Post hoc analyses suggested benefit of stricter control on stroke in patients under age 75 and an adverse interaction with stricter control in patients over age 75. The Valsartan in Elderly Isolated Systolic Hypertension (VALISH) study examined achieving SBP <140 mmHg to SBP of 140-149 mmHg in patients aged 70-84 years. [15] No difference between achieving mean SBP of 136.6 vs. 142 mmHg was seen in the primary composite cardiovascular event endpoint after 3 years. These data do not support benefits of achieved mean blood pressures of 137 mmHg compared to 140-149 mmHg. Those promoting lower SBP goals , cite the non-randomized Cardio-Sis study that reported multi-system surrogate endpoint composite benefits of tight control (SBP <130 mmHg) compared to "usual control" of <140 mmHg by primary caregivers in 1110 patients over age 50 years with and without prior CVD (one third > age 70; few over 75 years). [16, 17] The data are difficult to evaluate as there was significant overlap between groups in SBP achieved, only surrogate endpoints that included left ventricular hypertrophy were examined. In addition, few people were over age 75 years limiting the extrapolation to older people. It and other similar trials serve mainly to demonstrate the safety of a 130 mmHg systolic target in a clinical trial. [18] Several ongoing trials address target SBP levels for maximum benefit on cardiovascular composite endpoints (Systolic Blood Pressure Intervention Trial (SPRINT) or on stroke in patients with prior stroke or TIA (European Society of Hypertension-Chinese Hypertension League Stroke in Hypertension Optimal Treatment randomized trial). [19]

Non-cardiovascular endpoints. Cognitive effects of SBP lowering have been evaluated in several trials. In the Systolic Hypertension in Europe (Syst-EUR) trial, NNT was 50 at 5 y follow-up to prevent worsening cognition in one older person. In contrast, the Systolic

Hypertension in the Elderly Program (SHEP) reported a 0.3% between group difference, the HYVET trial of patients over age 80 did not find a benefit of treatment over placebo at 2 years, nor did the SCOPE trial of patients over the age of 70. Several meta-analyses and a Cochrane review concluded no evidence for benefit [20] while others combining data from randomized hypertension treatment studies concluded a hypertension treatment advantage. [21] The varying results suggest a small beneficial effect at most that may vary by drug. [22]

B. Guidelines.

The diastolic target is <90 mmHg but the optimal systolic target is a matter of debate. [23] Although there are little new data from large studies of the treatment of hypertension in the elderly, more recent guidelines no longer advocate lowering systolic blood pressure to less than 140mmHg Table 2 presents SBP targets from a number of sources. The Eighth Joint National Committee (JNC) Panel Members stated goal is < 150/90 mmHg for *all* people over age 60 years to more closely approximate the blood pressures achieved in the trials showing benefit and in contrast to earlier JNC recommendations of <140/90 mmHg that were based on the targets for the trials and not the achieved blood pressures. [24] Canadian and NICE guidelines recommend SBP <150 mmHg in people over age 80 (without diabetes or target organ damage) and <150/90 mmHg in younger patients. [25, 26] This reflects the greater emphasis on randomized placebo-controlled data as the level of evidence on which to base guidelines and using the blood pressure levels achieved in the trials rather than stated trial targets for recommendations, increasing recognition of potentially altered risk-benefit relationships in the oldest patients, and a move to "patient-centered" goals of therapy rather than population-based non-individualized care. Targets are the same for women and men despite lower systolic pressures in women at earlier ages.

The 2014 U.S. and 2013 ESH/ESC guidelines provide initial drug recommendations that do not differ based on older age (thiazide-type diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB)). Canadian guidelines recommend thiazide-type diuretics, long-acting calcium channel blockers or ARB's for isolated systolic hypertension and NICE guidelines recommend calcium channel blockers in those over age 80. [24-27] Beta-blockers are not considered first-line therapy in the absence of non-hypertensive indications in most of the guidelines and ACE and ARB combinations are to be avoided.. To date, most older patients have required more than one pharmacologic agent to reach SBP targets less than 140 mm Hg.

C. Adverse Effects. Individual antihypertensive agents will not be addressed, but monitoring for adverse metabolic effects, drug interactions, postural hypotension, constipation, urinary frequency or continence problems, and AV block or sinus node depression are important in the elderly. It has been shown repeatedly that the single most important factor contributing to all types of adverse drug interactions is the number of medications co-administered.[28] In the older person, especially, consideration of drug combinations that reduce the number of medications by treating multiple conditions should guide medication choices. A potential benefit of less stringent blood pressure targets in the very elderly may be use of fewer co-administered medications for blood pressure control and reduced polypharmacy.

An emerging concern is serious injuries due to falls. Major injuries from falls such as brain injury and hip fracture have an adverse effect on function and mortality in the elderly similar to that of cardiovascular events but have not been part of adverse events compiled during large clinical trials. Several studies of "typical" older patients with co-morbid conditions report increased risk of fall injuries with moderate intensity antihypertensive therapy as well as hip fracture during the weeks immediately following antihypertensive medication initiation. [29-31] Although further data are needed, greater attention to identifying older patients at higher risk for falls and avoiding postural hypotension is also needed.

Blood pressure targets and choices of agents may need to be reconsidered in the patient at increased risk for falls.

D. Perspective. There are clear benefits to treatment of systolic as well as diastolic hypertension in the elderly. Clinical trials have focused on use of pharmacologic agents and have not included investigations of salt restriction or intensive lifestyle modifications that might have fewer adverse effects. Pharmacologic blood pressure reduction reduces strokes after a period as short as one to two years, with less reduction of other cardiovascular events after 2-5 years, and potential improvements in memory decline after five years. The SBP target is less clear with no data showing benefits of achieving pressures under 140 mmHg in patients over 75 years of age and there is the possibility of harm. In healthier and more functional patients over age 75, systolic goals might logically be lower than in the more commonly encountered 80 year old with higher burden of disease or with frailty. [24, 32] (http://guidance.nice.org.uk/QS28-- 2013). Debate about optimal blood pressure targets will continue until there are more data on women, the very elderly, and ethnic minority groups.

3 Cholesterol Lowering

A. Data from Prevention Trials.

Secondary prevention trials have focused on selected groups of younger elderly (60-75 y of age) with CAD, at high risk for development of CAD, or with prior stroke. (see Table 3) The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study of those with or at high risk of CVD aged 60-72, showed benefits in a composite cardiovascular endpoint but no stroke benefit after 3 years. In the pivotal Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) secondary prevention trial of patients with prior stroke or TIA, few patients over age 75 were enrolled (0.15%). [33] Similarly, while increasingly lower LDL-cholesterol targets that require higher doses of statins are recommended in CAD guidelines (LDL-C less than 100 mg/dL), [34] the major trial on which these recommendations are based explicitly excluded patients over age 75 (Treating to New Targets (TNT) Trial) and enrolled primarily Caucasian men.[35]

Primary prevention trials of lipid lowering have not usually focused on the elderly. Examination of trial data (see Table 2) shows that Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS), West of Scotland Coronary Prevention Study (WOSCOPS),

Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), and PROSPER enrolled *no* subjects aged 75 years or older. A recent meta-analysis attempted to address whether statins reduce all-cause mortality or cardiovascular events in "elderly" people without established cardiovascular disease. [36] Data were combined from AFCAPS, Anglo-Scandinavian Cardiac Outcomes Trial: lipid-lowering arm (ASCOT-LLA), Collaborative Atorvastatin Diabetes Study (CARDS), JUPITER, and PROSPER that enrolled primarily younger elderly (see Table 2). The authors concluded that statins significantly reduced the incidence of MI and stroke but did not significantly prolong survival in the median 3.5 year study durations. Corrected estimates of NNT were 83 to prevent one cardiovascular event and 142 to prevent one stroke in people over age 65 years. [37, 38] A Cochrane Collaboration combined individual level data from older people enrolled in a larger number of "primary" prevention studies including studies with up to 10% of participants with CVD. [39] They estimated NNT of 196 to prevent one stroke, 56 to prevent any cardiovascular event, and 96 to prevent one death over 5 years. This is similar to the Cholesterol Treatment Trialists Collaborators analysis of individual data from 27 trials (average ages in the early sixties) of NNT of 167 to prevent one vascular event for people at lower risk of CV event within 10 year compared to NNT of 67 for those at higher risk. [40]

B. Guidelines.

Professional societies and government agencies have issued guidelines for management of LDL-related risk that vary in ways to calculate risk as well as lipid targets and treatment practices. [41] The recent ACC/AHA guideline does not make primary prevention treatment recommendations for people over age of 75 in view of the absence of randomized placebo-controlled data. [42] The American Association of Clinical Endocrinologists and AHA Women's Cardiovascular Disease Prevention Guidelines recommend the Reynolds Risk Score in women, derived from women under 60 years of age followed for 9.6-10.2 years [43] The Canadian Society recommends the Framingham risk score and treatment of those at high risk (over 20% risk) with LDL-cholesterol over 135 mg/dL and consideration of treatment for intermediate risk with LDL-cholesterol over 135 mg/dL. [44] The Joint British Societies defer to 2014 NICE guidelines that advocate treatment at $\geq$ 10% risk estimated by the Q-Risk2 calculator in patients up to age 84. [45, 46] NICE guidelines acknowledge the absence of data in adults over age 85 but conclude it

appropriate to consider statin use for elevated LDL-cholesterol as risk of CVD events may be higher in this group. Recognizing the higher burden of co-morbidities, decreased renal function and more co-medications in the very elderly, they recommend 20 mg atorvastatin for primary prevention. [46] Guidelines for both primary and secondary prevention state that decisions regarding statin therapy be made after an informed discussion between clinician and patient about risks and benefits of treatment. ACC/AHA guidelines suggest that moderate intensity statin therapy be considered for individuals >75 years of age with clinical ASCVD based on limited trial data showing benefit in primarily older male participants likely to be healthier than many older individuals presenting for clinical care and stress individualized decision making in these patients. [42]Potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy are identified as treatment considerations. [46]

C. Adverse Effects.

Use of statins in clinical practice has been associated with higher rates of side effects and intolerance than in clinical trials. The most frequent complaints are related to muscle. Myopathy is more common in those over 80 years of age, in women compared to men, with multiple co-morbidities (including chronic renal insufficiency, esp. due to diabetes), and with higher doses. It has been reported that 10.5% of patients have muscular symptoms with statins that required analgesics in 39%, with 38% unable to perform moderate exertion, and 4% confined to bed or unable to work.[47] Cross-sectional studies of adults report 22-23% with musculoskeletal pain during statin use.[48] Estimates of the incidence of myopathy varies widely and are unlikely to be determined from randomized trials as many had a statin tolerance run-in phase or excluded patients with prior reports of statin intolerance. [49]

The JUPITER trial brought to light an increased risk of new diabetes in statin-treated vs. placebo-treated patients. [50] A Cochrane meta-analysis combined these data with AFCAPS/TexCAPS data to estimate a significant relative risk of developing diabetes on a statin of 1.18 or a number needed to harm of 235. [39] Other meta-analyses report slightly different estimates depending on dose or statin intensity. [51] While some argue that population

cardiovascular benefit is outweighed by the risk, patients may expect not to be harmed by a "preventive" treatment.

In SPARCL and ASCOT-LLA, increases in hemorrhagic stroke rates were seen with atorvastatin despite net decreased stroke risk, with older age associated with an increased hemorrhagic stroke risk. [39] Adverse cognitive effects have been described as the second most common complaint of patients taking statins in the community.[52] There are also reports of reversible impaired cognition or worsening of dementia in older patients treated with statins [50, 53] and while causation is debated, manufacturers have added an FDA-mandated warning to statin prescribing information. A less well recognized and less common adverse effect is peripheral neuropathy. Evidence has emerged primarily during post-marketing experience as no randomized trial analyzed peripheral neuropathy as a major adverse effect of statins. It is estimated to occur in about 1/2200 patient years and be associated with duration of exposure that is inversely related to reversibility. [54, 55]

D. Perspective. Primary prevention data with statins in people over the age of 75 are extremely sparse and many prevention trials enrolled patients with prior cardiovascular disease such that no high level of evidence recommendations can be made. Data show that older patients decide against choices that impact on their quality of life, such that activity-limiting muscle pain, adding diabetes management, medications, and potential complications or the risk of increased cognitive decline may be considered undesirable for uncertain benefit.[56] The immediate risk of side effects from statins is on the order of 12-20% in typical older patients outside of clinical trials and reduction in risks and the benefits may not accrue for at least 3-5 years. There is a rationale for use of lipid lowering therapies in older patients with at least a 3-5 year estimated lifespan and a significant cardiovascular event risk of at least the same magnitude as the risk of side effects in the near term if the patient wishes to use this preventive measure after discussion of the potential risks and benefits. There is little rationale to treat the older patient at low risk. However, a major challenge is the lack of agreement on how to define the magnitude of risk in the very elderly, and especially older women that comprise the majority of very elderly.

Exercise.

A. Prevention Trials. There are no large or long-term studies of exercise for cardiovascular disease prevention initiated in older patients. Epidemiologic and cross

sectional studies show an association between higher levels of physical activity and lower rates of cardiovascular disease. [57] Analyses of the over 10,000 older adults participating in the Established Populations for Epidemiologic Studies of the Elderly showed an almost 2-fold increased likelihood of dying without disability among the most physically active compared with the sedentary. [58] Initiating physical activity even at older ages has been reported to improve longevity [59] A recent analysis of Framingham participants reported decreases in cardiovascular disease with long-term (40 y) greater physical activity compared to low physical activity. [60] Data also show significant reduction in falls, increased walking speed, greater ability to perform activities of daily living and reduced physician visits and hospitalization rates in older adults with higher levels of physical activity or after trials of aerobic or resistance exercise in elderly with falls or frailty. [57] Exercise intervention studies in older people have also shown reductions in triglycerides. LDL-cholesterol and non-HDL-cholesterol, increased HDL-cholesterol concentrations, reduced arterial stiffness, improved endothelial and baroreflex function, and increased vagal tone.

B. Guidelines. Recommendations [57] are currently the same for all people over the age of 65 years. U.S. and Canadian guidelines for healthy people over the age of 65 advise at least 150 min of moderate- to vigorous-intensity aerobic physical activity per week, in bouts of 10 min or more, state benefits of adding muscle- and bone-strengthening exercises that use major muscle groups at least 2 days per week and for physical activities to enhance balance and prevent falls in those with poor mobility. [61] and (http://www.health.gov/paguidelines/guidelines/chapter5.aspx).

C. Perspective. While randomized double-blind placebo or attention-controlled trials of exercise to prevent cardiovascular events have not been performed, data suggest improved lifespan and cardiovascular health with higher activity levels, improvements in daily functioning, decreased falls, and the absence of harm. Incorporation of exercise into the preventive care of the older person can be supported for overall benefit.

Aspirin.

A. Prevention Data. Low dose aspirin is a part of the secondary prevention regimens after heart attacks and strokes in the absence of contraindications to aspirin independent of age. Completed and ongoing primary cardiovascular disease prevention trials of aspirin have

recently been reviewed elsewhere. [62, 63] From studies reporting favorable effects of aspirin, it appears that if 10,000 people took daily aspirin for 10 years, about 72 major cardiovascular events, would be prevented on average. These estimates are based on studies of average duration of 3.7-10 years. Data from completed trials, however, are from mostly middle-aged people (mean ages of under 65) at low cardiovascular risk and data have not been presented stratified by age or cardiovascular risk. Ongoing studies have enrolled people over age 70 years but results are not currently available.

B. Guidelines. The lack of clinical trial data has resulted in disparate recommendations for aspirin ranging from guidelines that do not recommend use of aspirin (or clopidogrel) in individuals without disease due to the increased risk of major bleeding to guidelines that support use of low dose aspirin in all persons age 50 and older without cardiovascular disease.

C. Adverse effects. The most common adverse effect with aspirin is bleeding. About 46 to 48 of 10,000 people taking daily aspirin for 10 years will have major bleeding (requiring transfusions or causing death) and 117 to 182 will have less serious gastrointestinal bleeding. Hemmorhagic stroke risk is also increased with use of aspirin and the relative risk attributed to aspirin of about 1.84 is higher than that with statins.

D. Perspective. Older people have increased risks of bleeding as well as increased risks of heart attacks and stroke. The balance between potential benefits and risks of aspirin differs in each person as do preferences about acceptable risk to prevent something that might or might not happen in the future. The older person most likely to have cardiovascular benefit from aspirin is someone at higher cardiovascular risk with preserved functional abilities and who also has a low or acceptable risk of bleeding and a life expectancy in the range of time to benefit in trials, notably higher than for the treatment of hypertension or elevated lipids. The older person at very low risk for heart attacks or stroke is unlikely to have cardiovascular benefits but may have bleeding. For older people with increased risk of cancers, an additional consideration is the growing evidence for anti-cancer effects of aspirin that accrue over 3-5 years (while bleeding risk is immediate). [64]Decisions should be individualized based on total disease risk, lifespan considerations and potential aspirin benefit.

CONCLUSIONS

There are limited gold standard data on which to base decisions for primary prevention in the "typical" older patient over the age of 75 years encountered in daily practice. Potential benefits and adverse effects of preventive measures must be considered within the expected lifespan of the older patient and incorporate patient preferences. In older and very old patients, therapeutic goals shift from life prolongation to a focus on quality of life and maintaining function. Treatment of hypertension has cardiovascular benefits within 2 years for prevention of stroke that will be within the anticipated lifespan of many if not most people 75 years of age and older and lifestyle and multiple medication choices are available. There is agreement on the target diastolic blood pressure of <90 mmHg but systolic targets need to be individualized for the patient with suggested targets of <140 -145 mmHg in younger healthier elderly to <150 mmHg in the oldest patients or those with multiple co-morbidities or increased fall risks. For treatment of hypercholesterolemia, time to benefit is longer and adverse effects of the most effective drugs are higher in the older patient mandating individualized decisions and greater emphasis on non-pharmacological approaches. Exercise can be tailored to the older persons functional status and has multiple health benefits and should be incorporated into health maintenance and disease prevention regimens. In contrast, aspirin for primary cardiovascular disease prevention in the elderly may have a more limited role due to bleeding risks. As the population over the age of 75 years is rapidly growing, guidelines that address the changes over the complete agespan of older adults and do not use arbitrary recommendations for all people over the age of 65 are needed.

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Figure Legend

Figure 1. Life expectancy estimates for older persons are shown by sex, co-morbidity, and functional status. Average life expectancy is represented by the solid black line. Data based on co-morbid status and for heart failure are from a sample of the Medicare population recently reported by Cho, et al. (3) Low/medium co-morbidity conditions were history of M.I., ulcer, acute M.I., rheumatologic disease, peripheral artery disease, diabetes, paralysis, cerebrovascular disease; high co-morbidity conditions were chronic obstructive pulmonary disease, heart failure, moderate/severe liver disease, chronic renal failure, dementia, cirrhosis/chronic hepatitis, AIDS). The shaded area represents the range of co-morbid conditions (no co-morbid conditions are represented by the green solid line; medium to low co-morbidity by the orange line, to high co-morbid health status represented by the solid red line. Heart failure data are represented by the solid blue line. Data based on functional status, are from the Established Populations for Epidemiologic Studies of the Elderly as reported by Keeler, et al. (4) ADL= activities of daily living bathing and showering, dressing, Eating/feeding (including chewing and swallowing), Functional mobility (moving from one place to another while performing activities), personal hygiene and grooming (including brushing/combing/styling hair) and toilet hygiene; mobility impaired was defined as inability to walk half a mile and/or walk up a flight of stairs without help. Total independent status is represented by the green dashed line, mobility impairment by the brown dashed line, and ADL impairment by the red dashed line. Life expectancy declines as age increases but varies by sex, co-morbidities and functional status. Life expectancy is shortest in those with heart failure and in those with impairment in ADLs and longest in those without co-morbidities who function independently.

Figure

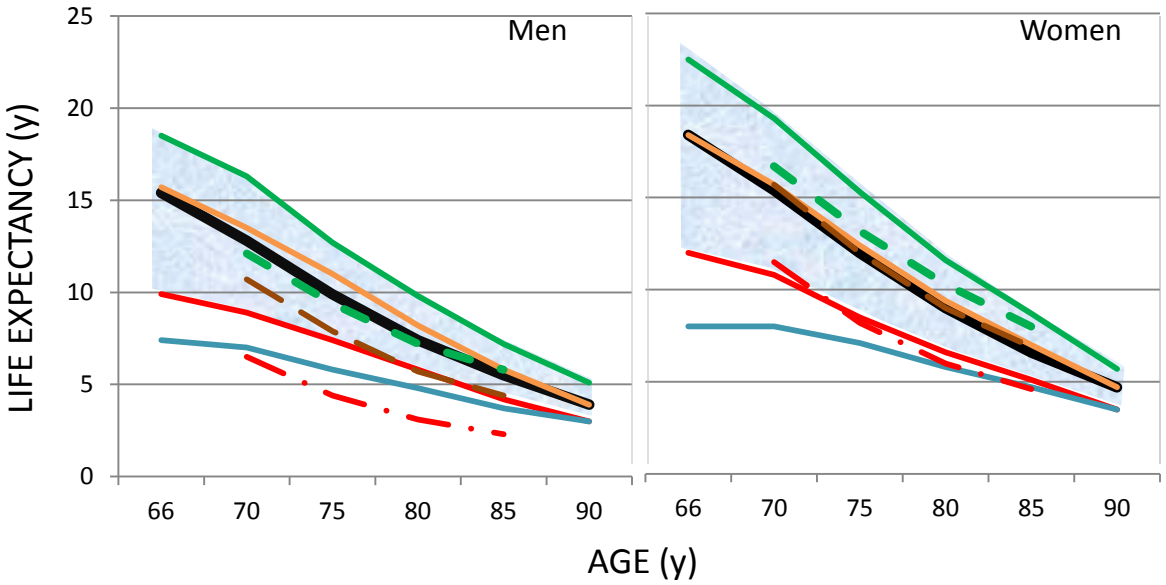

Table 1

Table 1. Randomized Placebo-controlled trials of Blood Pressure Reduction in the Elderly including patients over the age of 75 years

						Risk Reduction (%)			
Trial (n)	Duration (y)	Enrollee Ages (y)	Type of Hypertension	Drugs	Achieved Systolic BP (mmHg)	Stroke (NNT)	Coronary Artery Disease	Heart Failure	All Cardiovascular Disease (NNT)
EWPHE (65) (840)	4.6	>60	Diastolic ± Systolic	HCTZ + TR (+)	NR	36 (24)	20	22	29
Coope (6)(884)	4.4	60-79	Diastolic ± Systolic	Beta (ATEN) (+)	170 vs 190*	42 (20-21)	-3	32%	24
STOP-HTN(7) (162)	2	70-84	Diastolic ± Systolic	HCTZ+Am or Beta	NR	47 (34)	13	51	40
SHEP (8) (4736)	5	>60 70-79 (45%) >80 (14%)	Systolic	Chlor	144 vs. 155	33 (32)	27	55	32 NS (195)
Syst-Eur(9) (4695)	2	>60 Mean70±6.7	Systolic	CCB(NITR)	151 vs 161	42 (22)	26	36	31
Syst-Eur2(66)	5	see above	see above	see above	NR	NR	NR	NR	Reduced (50-60)
STONE(67) (1632)	2.5	60-79	Systolic	CCB (NIF)	146.4 vs 155.7	57 (38)	6	68	60
Syst-China(11) (2394)	2	≥ 60	Systolic	CCB(NITR)	150.7 vs 159.3	34 (64)	33	38	37
SCOPE(12) (4937)	3.7	70-89 70-79 (79%) 80-89 (21%)	Systolic ± Diastolic Systolic only	ARB (CAND)	145.2 vs 148.5	24# (92) 42 (52)	NR	NR	11 NS
HYVET(10) (3845)	2	>80 80-84 (73%) 85-89 (22.4%) ≥90 (4.6%)	Systolic (33%) Systolic+ Diastolic (67%)	Indapamide ±ACE (PER)	143.5 vs 158.5	30	Nr	64	23

N= number of subjects. Chlor= chlorthalidone; HCTZ=hydrochlorothiazide; TR=triamterene; Beta= beta-blocker; ATEN=atenolol; Am=amiloride; CCB=calcium channel blocker; NITR=nitrendipine; NIF=nifedipine; ARB= angiotensin receptor blocker; CAND=candesartan; PER=perindopril; *At end of trial active treatment vs. placebo. # risk reduction was greatest in patients with history of prior stroke. NR=not reported. NS=not statistically significant.

Table 2

Table 2. A Comparison of Guidelines for Hypertension Diagnosis and Treatment in the Elderly

	Threshold for Treatment	Systolic Blood Pressure Treatment Target*	Recommendend Initial Agents
ADA(68)	140 /90	< 140/80 Age >80: Not stated but based on function <150/90 if long-term care, end-stage chronic illness, or moderate to severe cognitive impairment or dependent in ≥ 2 ADL's	ACE or ARB
AHA/ACC(69)	140/90	Age >80: Not stated	Thiazide
AHA/ACC elderly (32)	140/90	Age 65-79: <140 >80: 140-145 (if tolerated	Any agent
ASH/ISH(70)	150/90	Age ≥ 80: <150/90	CCB or thiazide (age >60)
Canadian(71)	>160/90	Age ≥ 80: <150	Thiazide, long-acting CCB, or ARB
ESC/ESH 2013(27)	≥ 160	Age <80: 140-150 (<140 can be considered in fit only) >80: 140-150 (fit and cognitively intact	Thiazide, CCB, ACEI, or ARB
JBS3(45)	≥140/90, office > 135/85 ambulatory daytime mean	Age Clinic Ambulatory/home daytime mean 65-79: < 140/90 <135/85 >80: <150/90 <140/85	CCB for Age > 55 y
JNC 8 Panel Members-2014(24)	140/90	Age All >60: 150/90	Any class for non-blacks For blacks: CCB or thiazide

*In absence of diabetes or severe renal failure and modified for significant co-morbid states

Table 3. Randomized Placebo-controlled Cholesterol Lowering Trials for the Prevention of Cardiovascular Disease in the Elderly

Primary Prevention	**Particpants Characteristics**	**(n)**	**Per Cent >75 y.** Age range (% women, n)	**Intervention**	**Outcomes (timeframe)**	**NNT***
JUPITER (72)	LDL <130 md/dL , CRP>2 mg/dL	17,802	**None** 60-71y (38 % ,6801) 25% minority	Rosuvastatin (20 mg) vs placebo	Reduced risk for MACE (median 1.9y, maximum 5y) Increased risk of Diabetes	95 for 1 event at 2 y
WOSCOPS(73)	No CHD High Cholesterol	6595	**None** 45-64y (0, 0)	Pravastatin (40 mg) vs placebo	Reduced coronary events and coronary mortality (5 y) no stroke benefit) (median of 5.2 y)	42 for 1event at 5 y
AFCAPS Tex-CAPS(74)	No CHD	6605	**None** 45-73y (15%, 997)	Lovastatin vs Placebo	Reduced risk of first major acute coronary coronary event (5.2y)	49 for 1 event at 5.2 y
ALLHAT-LLT (75)	Hypertension + one additional CVD risk factor	10,355	n.a., 50% >65y Mean: 66±7.6 y (49%, 5051) 40% minorities	Pravastatin (40 mg/day) + anti-HTN	No significant reductions in mortality, CHD or stroke vs. usual care (4.8y)	n.s. (4.8y)
ASCOT-LLA (76)	Hypertension + three additional CVD risk factor	10,305	n.a.,64%>60 Mean:66±8.5 y (19%, 1942)	Atorvastatin (10 mg/day) + anti-HTN	Reduced stroke risk and MACE risk (3.3y) If stroke, increased hemorrhagic women without benefit	164 for 1 (3.3 y) 94 (3.3 y)
Secondary Prevention						
SPARCL(33)	Prior Stroke or TIA No CHD LDL 100-190	4731	**<0.15%**, na 21-92y (40%)	Atorvastatin (80 mg) vs Placebo	Strokes reduced (4.5y) Increased hemorrhagic strokes Reduced coronary events	52 for l stroke

PROSPER (77)	CVD or high risk	5804	**None** 60-72y 0 (52%, 3000)	Pravastatin (40 mg/day)	Reduced composite endpoint of CHD death, nonfatal MI, and stroke; as well as CHD death plus nonfatal MI (3 y) No reduction in stroke	Crude NNT=59 (3y)

N= number of subjects. LDL=low density cholesterol. CHD=coronary heart disease. CVD=cardiovascular disease. TIA=transient ischemic Attack. CRP=C-reactive protein. *Number needed to treat. na=not available. Anti-HYP=antihypertensive medication. MACE= major acute coronary event